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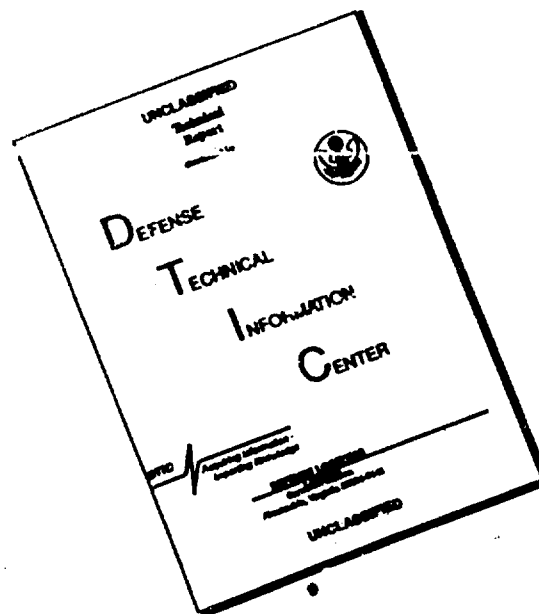
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Allergy Reactions in Persons Inoculated Cutaneously With Live Egg-yolk Tularemia Vaccine, by S. S. Dyachenko, O. P. Khyzhyns'ka, and S. H. Buyalo

Report to the scientific conference of the Microbiology Chair of the Kiev Medical Institute, 6 September 1950

The search for an effective prophylactic preparation to combat tularemia began as soon as the agent causing the infection was discovered. Vaccine prophylaxis could be of great significance, since the tularemia infection leaves strong immunity. The better the form of post-infection immunity the greater the opportunity for the formation of inoculation immunity. If the infection even under natural conditions leaves a poor form of immunity, inoculation prophylaxis may be difficult and even unsuccessful.

All attempts to obtain effective killed tularemia vaccine have been fruitless. It is now well known that inoculation immunity brought about by killed vaccines is often of poor stability and strength. And killed antitularemia vaccines have never caused immunity.

It is only Soviet scholars who have laid the theoretical groundwork and provided a brilliant solution to the problem of the specific prophylaxis of tularemia. N. Ya. Gayskiy, whose achievements have been recognized by the Soviet government, which awarded him the Stalin Prize, was the first to prepare live tularemia vaccine. Gayskiy discovered the laws governing infection and immunity in experimental tularemia. He showed that the weakly virulent immunogenic cultures of the tularemia bacillus caused immunity in animals, and established a similar law for humans. Thus a person may become immune not only through the transfer of a clinically developed disease, but also as a result of

inoculation with a weakened strain of tularemia microbe. In order to create active immunity one may use immunogenically fully active strains. One of the features of the immunogenically fully active tularemia microbe is its outstanding infectiousness for those animals most sensitive to tularemia infection (white mice) and its low virulence for humans and less sensitive animals (guinea pigs and rabbits). A single injection of such a culture into the proper animals makes them able to resist a virulent tularemia culture independently of the dose and the method of injection.

It has been shown that tularemia vaccine cultures cause an immuno-allergic transformation of the organism, which is a symptom of immunity, similar to the transformation of the organism following recuperation from tularemia.

B. Ya. El'bert has demonstrated the possibility of cutaneous vaccination against tularemia. The Soviet government, appreciating the value of his experiments, has awarded him the Stalin Prize. The technique of rubbing the vaccine into a cut in the skin, similar to smallpox inoculation, makes possible the mass use of this procedure when necessary.

In a short time Soviet scholars have made a detailed study of the methods of producing and using live tularemia vaccine, and have shown its epidemiological effectiveness (Gayskiy, Gayskiy and his co-workers, El'bert, Seleznev, Faybich, Dzhanpoladova, Sil'chenko, Altareva, Borodin, Chernina, Dons'kykh and Chelisov, Moroz and Khyzhyn's'kn, and others).

Tularemia is one of the infections which cause a state of increased sensitivity to material stimuli, a state which may last for some time.

One of the best indications of the protective transformation of the organism after inoculation with tularemia vaccine is the allergy test. A

positive intradermal allergy test for tularin is also an indication that tularemia has been transferred and that stable immunity has been developed to this infection.

In our work we have presented the results of our studies of the permanence of the intradermal allergy reaction after cutaneous vaccination with egg-yolk tularemia vaccine.

#### METHOD OF OPERATION

In eight inhabited places people of various ages and sex were vaccinated. predominantly adults from 20 to 40 years old. They were vaccinated cutaneously with live egg-yolk vaccine. On an egg-yolk medium the causative agents of tularemia grow profusely and retain their viability over a considerable period of time. The vaccine used was that of the Rostov State Counterepidemic Institute. Twelve (sic) series were used, with the following numbers: 141, 145, 171, 179, 190, 192, 195, 250, 256, 126, and 158. The allergy test was performed at random on the vaccinated population, and the nature and course of the reactions studied.

The allergin used for the intradermal reaction was "Mikrob" tularin from the Saratovsk State Counterepidemic Institute, containing 100 million microbe bodies per milliliter. series No. 16.

After the skin had been prepared, each person received in the forearm a cutaneous injection of 0.1 milliliter of vaccine, representing 10 million microbe bodies.

Previous experiments had indicated that within 6-8 days after inoculation the allergy test would be positive for 24-48 hours. The intradermal allergy test was considered positive when around the point of tularin injection there was a reddening of the skin measuring from 1 x 1 by 5 x 4 centimeters, with

various degrees of swelling of the skin.

The control in all these cases was the presence or absence of changes following the injection of a standard dose of the same type of tularin in persons who had received a tularemia injection in the recent past, revaccinated persons, and healthy persons whose medical history included no tularemia infection and who had not been vaccinated.

The allergy reaction was tested twice - in 24 and in 48 hours.

#### ACTUAL OBSERVATIONS

We observed both the duration of allergy reactions and the clarity with which they appeared. By the duration of the reaction we mean the time passing from the day of vaccination to the day the allergy test is performed. Data are presented below on our observations from one month to two years.

The extent to which dermal reactions appeared were denoted by plus signs: sharply positive reactions received three plus signs, positive reactions two plus signs, and weakly positive reactions one plus sign.

The duration of the allergy test was studied on 1,126 persons inoculated in the autumn months of 1948 and the spring of 1949. The results of these investigations are given in the table.

Duration of Intradermal Reactions to Tularin

<u>Item</u>	<u>Number of Months Since Inoculation</u>							<u>Total</u>
	<u>7</u>	<u>12</u>	<u>14</u>	<u>15</u>	<u>16</u>	<u>18</u>	<u>24</u>	
Number of persons examined	58	170	617	111	24	81	65	1,126
Sharply positive								
Absolute number	24	16	128	17	4	32	4	225
Percent	41.4	9.4	20.8	15.3	16.7	39.5	6.2	20.0
Positive reactions								
Absolute number	31	96	301	82	17	41	25	593
Percent	53.5	56.5	48.8	73.9	70.8	50.7	38.4	52.7
Weakly positive reactions								
Absolute number	1	26	96	3	0	4	14	144
Percent	1.7	15.3	15.5	2.7	0	4.9	21.6	12.8
Negative reactions								
Absolute number	2	32	92	9	3	4	22	164
Percent	3.4	18.8	14.9	8.1	12.5	4.9	33.8	14.5
Total, sharply positive and positive								
Absolute number	55	112	429	99	21	73	29	818
Percent	94.8	65.9	65.5	89.2	87.5	90.0	44.0	67.2

<u>Control</u>	<u>Recovered</u>	<u>Revaccinated</u>	<u>Healthy, not Vaccinated</u>
<u>Item</u>			
Number of persons examined	10	9	10
Sharply positive reactions	3	2	--
Positive reactions	3	4	--
Weakly positive reactions	--	1	--
Negative reactions	4	2	10
Total, sharply positive & positive	6	6	--

The material presented shows that within this period the intradermal test was positive in 962 (85.5 percent) of the 1,126 persons examined, and negative in 164 persons (14.5 percent). Of this total of 962 persons with positive tests 225 (20.0 percent) gave sharply positive reactions, 593 (52.7 percent) positive reactions, and 144 (12.8 percent) weakly positive reactions. A sharply positive reaction is characterized by the following symptoms: sudden reddening, infiltration, painfulness to touch, and sometimes the formation of a small necrotic ridge at the point of injection of the tularin. In individual cases the following general reaction was formed: light headache, general indisposition, 2-3 degrees of fever, and enlargement and pain in the lymph glands. These symptoms disappeared in 1-3 days.

To provide control, the intradermal allergy test using tularin was performed on ten persons who had recovered from tularemia, on nine persons vaccinated with tularemia vaccine, and on ten immunized persons.

Of the ten persons who had recovered from the disease one had been sick in 1949 and eight in 1948 with visceral tularemia. One person had had the bubonic form of tularemia in 1949. It can be seen from the table that of



those who had recovered from the disease three gave sharply positive, three positive, and four negative reactions to the injection of tularin.

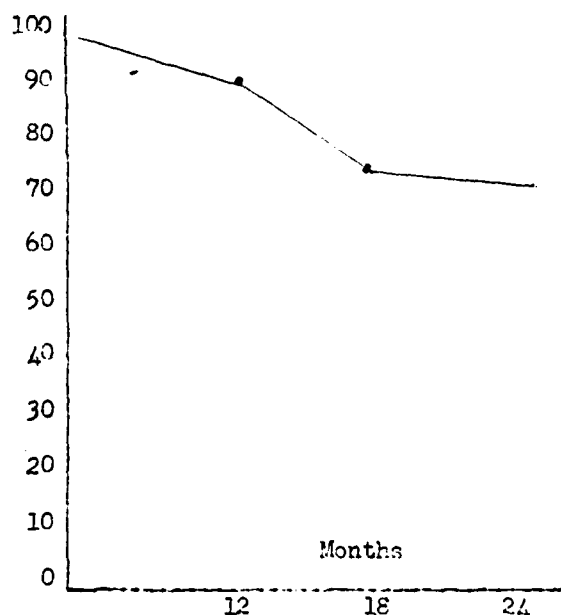
Of the nine persons revaccinated two were revaccinated 7 months, six 8 months, and one 10 months after the first vaccination. It should be pointed out that the reaction gave no sharp local or general reactions of the organism. The results of a recheck one year after the intradermal allergy test were: two persons gave sharply positive, four gave positive, one gave a weakly positive, and two gave negative reactions.

All ten healthy nonimmunized persons gave no reaction at all to the intradermal injection of tularin.

An analysis of the duration of intradermal reactions with respect to time of inoculation shows that they diminish with time. Seven months after inoculation they were positive in 56 (96.5 percent) of 58 cases, and after 24 months in 43 (66.1 percent) of 65 cases.

The table also shows the intensity of the intradermal reaction as a function of time of vaccination. Taking into consideration only sharply positive and positive reactions, they were found in 818 (72.7 percent) of 1,126 persons examined. The smaller the number of months since inoculation the larger the percentage giving these reactions. After 7 months these reactions were found in 55 (94.8 percent) of 58 cases, and after 24 months in 29 (44.5 percent) of 65 cases. At other intervals these reactions were found as follows: after 12 months in 112 (65.8 percent) of 170 cases; in 14 months in 129 (65.5 percent) of 617 cases; in 15 months in 99 (89.2 percent) of 111 cases; in 16 months in 21 out of 24 cases; and after 18 months in 73 (90 percent) of 81 cases. The figures given for each period of examination

are not identical, and they can be compared only under special conditions. Therefore if we take a longer period, such as 6 months, the reduced intensity of the reactions is quite clear. A graphic indication of the reduced reaction is to be found in the curve given in the figure below.



Percentage of intradermal reactions  
examined over a period of two years

The persons examined from 3 to 12 months after inoculation gave positive test results in 94.8 percent of cases, while those examined from 12 to 18 months after gave 71.6 percent positive results, and those from 18 to 24 months after gave 69.8 percent positive test results.

We succeeded in part in studying the effect of the various series of vaccines on the results of the intradermal reactions. We collected the vaccines under identical conditions and used them according to the same technique. Of the 12 series of vaccines three (series Nos. 126, 168, and

179) were used in separate populated points. Their effectiveness compared with that of other series was considerably greater.

#### DISCUSSION OF RESULTS

Tularemia is one of the infections which give rise to a profound transformation of the organism and a lasting and stable immunity to the given disease.

Of the vaccine preparations now in use the most effective are live vaccines prepared from the corresponding weakened (attenuated) strains. Live vaccines cause in the organism a profound reaction, expressed in the latent form of the infection. Such a reaction, of course, provides for the formation of excellent postinfection immunity, whose effect approaches that of immunity following recuperation from the disease.

The advantage of live over killed vaccines is particularly clear in cases in which killed vaccine shows no effect, such as in tularemia.

Finally, the great significance of live vaccines lies in the fact that they are applied only once; this makes possible their mass application. Live vaccines also give a rapid immunizing effect. Thus vaccination with live vaccines is not only a prophylactic but a counter-epidemic procedure available for wide use.

In this investigation in evaluating the cutaneous use of the tularemia vaccine we have limited our work to the intradermal reaction, which is a symptom of the allergic transformation of the organism. The intradermal test is one of the essential symptoms of the interaction of macro- and microorganisms in the infection process, both following clinical recuperation and as a result of the reactions of the organism to live tularemia vaccine.

Allergic reactivity is a more profound indicator of the immunological transformation of the organism in the disease process or of prophylactic immunization than is the agglutination reaction. It may also be used as a relative indication of immunity.

The intradermal test is in the overwhelming majority of cases accompanied by an opsonic-phagocytic reaction and the agglutination reaction in persons who have been inoculated cutaneously with live egg-yolk tularemia vaccine (Moroz, Khyzhyns'ka). This has also made it possible for us to limit our efforts to evaluating the vaccine solely by the intradermal reaction.

The material presented shows that an allergic transformation of the organism results from the cutaneous introduction of live egg-yolk-tularemia vaccine. This transformation is specific, since it occurred and developed almost identically in both recuperated and revaccinated persons, being negative in healthy, unimmunized persons. The vaccination process proceeds easily.

A comparison of the duration of the reaction at various intervals reveals certain regularities. The shorter the period of time (measured, in our experiments, in months) since inoculation the more clear and intense the intradermal reaction, while the more time had elapsed since inoculation the more rapidly the reaction diminished. One may speak of the dynamics of attenuation of the allergy reaction. Over a period of two years (the period of our investigations) in nearly one-half of the cases with sharply positive and positive reactions the reaction became feeble or quite negative. But in almost one-half the cases the reaction remained sharply expressed even after two years.

These observations on a large number of persons confirm the belief of Gaytskyi and his co-workers that the intradermal reaction - the allergy test -

lasts for a long time. We cannot say how long the reaction may last, since we are still making observations. Therefore the established fact, that the allergy reaction lasts up to two years in one-half the cases, provides a basis for the broad-scale use of this preparation as the most favorable counterepidemic agent. This is even truer since the allergy reaction may be used as a relative indication of the protective transformation of the organism. Thus, on the basis of our material, the need for revaccination may arise somewhat over two years after vaccination, depending on epidemic requirements.

Definitive conclusions on the dynamics of the attenuation of the reaction require observations of larger numbers of persons in each period of investigation.

There exists the observation, or rather the impression, that the individual series of vaccines used play a certain role. The vaccine series Nos. 126, 158, and 179 in the majority of cases showed a sharper allergy reaction than the other series of vaccines used. Further investigations and observations are necessary in order to evaluate each series of vaccine, but the approximate identity of other conditions has drawn our attention to this discrepancy. Changes may also occur during the technological process of preparing the vaccines, collecting and transporting them, etc. In the use and evaluation of vaccines the significance of the individual series must also be taken into consideration.

#### CONCLUSIONS

1. Live egg-yolk tularemia vaccine used cutaneously causes in the human organism the same special intradermal allergy reaction to tularemia as does transferred tularemia itself.

2. The intradermal allergy reaction as a response to live tularemia

○ vaccine is a specific reaction, since it was positive only in persons who had recovered from tularemia, who were revaccinated, and who had received cutaneous vaccinations.

3. The intradermal allergy reaction to tularemia was distinguished by sharpness during the entire period of observations, in the following proportions: during the first month after vaccination up to 95 percent, and at the end of the 24th month up to 44.5 percent.

4. Revaccination may be used within two years, depending on epidemic requirements.

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